CLINICAL PRACTICE

Vitiligo

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A healthy 25-year-old brunette woman reports a 12-month history of skin depigmentation. She first noticed patches of skin whitening on her hips; her physician prescribed an imidazole cream for a presumed fungal infection, but there was no improvement. After a vacation at the beach, she noticed additional depigmented patches on her elbows, shins, upper eyelids, and lower chin. A dermatologist made a diagnosis of vitiligo and recommended a sunscreen but offered little hope for treatment. She feels stigmatized by her appearance. How should she be evaluated and treated?

THE CLINICAL PROBLEM

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Vitiligo is the most common depigmenting disorder, with a prevalence of approximately 0.5% in the world population. Almost half of patients with vitiligo present before 20 years of age. The two sexes are equally affected, and there are no apparent differences in rates of occurrence according to skin type or race.[1,2]

Nonsegmental (or generalized) vitiligo and segmental vitiligo have distinctive clinical features and natural histories (Table 1 and Fig. 1). Nonsegmental vitiligo is the most common form of the disease (accounting for 85 to 90% of cases overall), but segmental vitiligo, because it generally has an earlier onset, may account for 30% of childhood cases.[3] Both nonsegmental and segmental vitiligo can initially present as focal vitiligo, which is characterized by a small affected area (<15 cm^2).[4] On rare occasions nonsegmental and segmental vitiligo coexist, and in such cases, segmental lesions are less responsive to treatment.[5]

A loss of epidermal melanocytes is the pathologic hallmark of vitiligo.[5,6] In completely depigmented areas, inflammation is usually absent, but mononuclear cells have been identified at the margin of the depigmented areas in cases of nonsegmental vitiligo, especially in rapidly progressing disease.[7] The initial cause of nonsegmental vitiligo is still debated but appears to involve immunologic factors, oxidative stress, or a sympathetic neurogenic disturbance. In nonsegmental vitiligo, the upward migration of melanocytes 24 hours after mechanical trauma in perilesional areas highlights the importance of Koebner's phenomenon (a cutaneous disease-specific response to a nonspecific, usually traumatic, stimulus such as pressure or friction) in the pathogenesis of the disease. In segmental vitiligo, a neurogenic sympathetic disturbance is considered a key precipitating factor,[3] but observations also suggest a genetic anomaly restricted to the segment (mosaicism).

Some genes track with vitiligo in populations of European descent, either as part of an autoimmune diathesis or with vitiligo in isolation. In the autoimmune group, variants in the gene encoding NACHT leucine-rich-repeat protein 1, or *NALP1*, have recently been identified.[8]

Table 1. Typical Features of Segmental and Nonsegmental Vitiligo.

Segmental Vitiligo	Nonsegmental Vitiligo
Often begins in childhood	Can begin in childhood, but later onset is more common
Has rapid onset and stabilizes	Is progressive, with flare-ups
Involves hair compartment soon after onset	Involves hair compartment in later stages
Is usually not accompanied by other autoimmune diseases	Is often associated with personal or family history of autoimmunity
Often occurs on the face	Commonly occurs at sites sensitive to pressure and friction and prone to trauma
Is usually responsive to autologous grafting, with stable repigmentation	Frequently relapses in situ after autologous grafting
Can be difficult to distinguish from nevus depigmentosus, especially in cases with early onset	

STRATEGIES AND EVIDENCE

EVALUATION

Diagnosis

In patients presenting with patchy depigmentation, a thorough history and physical examination, including examination with Wood's lamp (Fig. 2), should focus on ruling out other disorders (Table 2). Occupational exposures may cause depigmentation or exacerbate underlying vitiligo.[10] In nonsegmental vitiligo, typical macules show homogeneous depigmentation and have well-defined borders. A loss of hair pigment is usually not seen until the late stages of the disease. A hyperpigmented rim at the interface of depigmented and normally pigmented skin is commonly seen after sun exposure. Pinpoint depigmentation may precede patchy depigmentation in rapidly progressing disease. Macules in segmental vitiligo may have a more irregular border and less homogeneous pigment loss than those in nonsegmental vitiligo.[4] In patients with dark skin, there can be prominent involvement of mucosae. Several disorders may be confused with segmental vitiligo, especially nevus depigmentosus[11] (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). It is rarely necessary to perform a skin biopsy to confirm the diagnosis.

Assessment

An assessment form created by the Vitiligo European Task Force (VETF) may be useful in evaluation (an updated version of the form is available in the Supplementary Appendix).[4] Patients should routinely be asked whether there is a family history of vitiligo and premature hair graying and whether there is a family or personal history of thyroid disease or other autoimmune diseases (e.g., alopecia areata, rheumatoid arthritis, diabetes, and pernicious anemia).[12] Halo nevi (nevi with surrounding depigmentation) are 8 to 10 times as common in patients with vitiligo as in the general population[9]; they should be discussed as part of the personal and family history taking and assessed during the physical examination (including examination with Wood's lamp in the case of fair-skinned patients). Multiple halo nevi are a marker of cellular autoimmunity against nevus cells and may indicate an increased risk of vitiligo in patients with a family history of the disease. Skin color and ability to tan should be noted (information on phototype is important in establishing a plan for phototherapy), as should the distribution of the vitiligo (including genital depigmentation, which patients may not report because of embarrassment) and its duration and level of activity (progressive, regressive, or stable over the previous 6 months). In some patients with nonsegmental vitiligo, an acceleration phase occurs, with rapid disease progression over a period of weeks to months, warranting more urgent intervention (e.g., a short course of corticosteroids). A scoring system for assessment of the extent of disease, its stage, and the degree of spreading[4] (whether the disease is progressing, stable, or regressing) is included in the VETF form in the Supplementary Appendix. Patients should

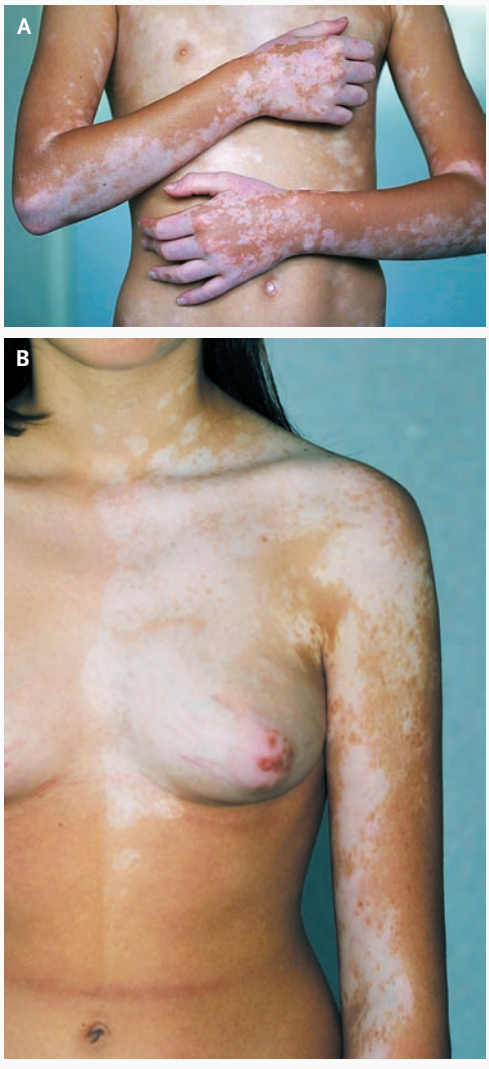

Figure 1. Nonsegmental and Segmental Vitiligo.

Nonsegmental vitiligo (Panel A) is characterized by white patches that are often symmetric and that usually increase in size over time, corresponding to a substantial loss of functioning epidermal melanocytes and sometimes hair-follicle melanocytes. Segmental vitiligo (Panel B) typically has a unilateral distribution that may completely or partially match a dermatome. In most patients there is one unique segment of depigmentation (Panel B), but in rare cases two or more segments with ipsilateral or contralateral distribution can be involved.

be asked about previous episodes of repigmentation, details of prior therapy and its usefulness, and any trauma preceding the skin changes (as in Koebner's phenomenon) (Fig. 3).[13] Patients should be asked about how vitiligo affects their daily life (e.g., as assessed on a visual analogue scale ranging from no effect to a large effect).

Because nonsegmental vitiligo is associated with an increased risk of autoimmune thyroid disease, especially Hashimoto's thyroiditis,[14] the thyrotropin level should be measured annually, especially in patients with antibodies to thyroid peroxidase at initial screening. The frequencies of associated autoimmune diseases in patients with vitiligo appear to vary with skin type or race.[15,16] Any symptoms or signs of organ-specific autoimmune diseases should prompt investigation.[17] A particularly high index of suspicion is warranted in patients with a personal or family history of autoimmune disease.

TREATMENT

In treatment studies, efficacy is typically assessed in terms of the proportion of treated patients in whom a specified degree of repigmentation is achieved, with more than 50% or more than 75%, depending on the study,[18] often considered a good response. However, these criteria are debatable insofar as complete repigmentation, especially in visible areas, may be needed for a high degree of satisfaction on the patient's part. Moreover, the evaluation of repigmentation is not well standardized.[19] A quantitative objective score (Vitiligo Area Scoring Index)[20] and the VETF score[4] have been proposed. Clinical photographs and, if possible, photographs taken under ultraviolet light are recommended for accurate monitoring of repigmentation.

Commonly used repigmentation therapies whose efficacy is supported by data from randomized trials include ultraviolet light (for the whole body or targeted to lesions) and topical agents (corticosteroids and calcineurin inhibitors). Camouflaging or depigmenting treatments (in widespread disease) are other options. Table 3 outlines stepwise treatment approaches. The involvement of a psychologist or psychiatrist may be helpful for patients who have difficulty coping with the diagnosis.

Ultraviolet Light

Narrow-band ultraviolet B (UVB) radiation, which delivers peak emission at 311 nm, is currently the preferred treatment for adults and children with nonsegmental vitiligo, as long as there is access to a specialized treatment center. In a randomized trial comparing the use of topical photochemotherapy (psoralen and ultraviolet A radiation [PUVA], a standard treatment in the past) with twice-weekly narrow-band UVB radiation

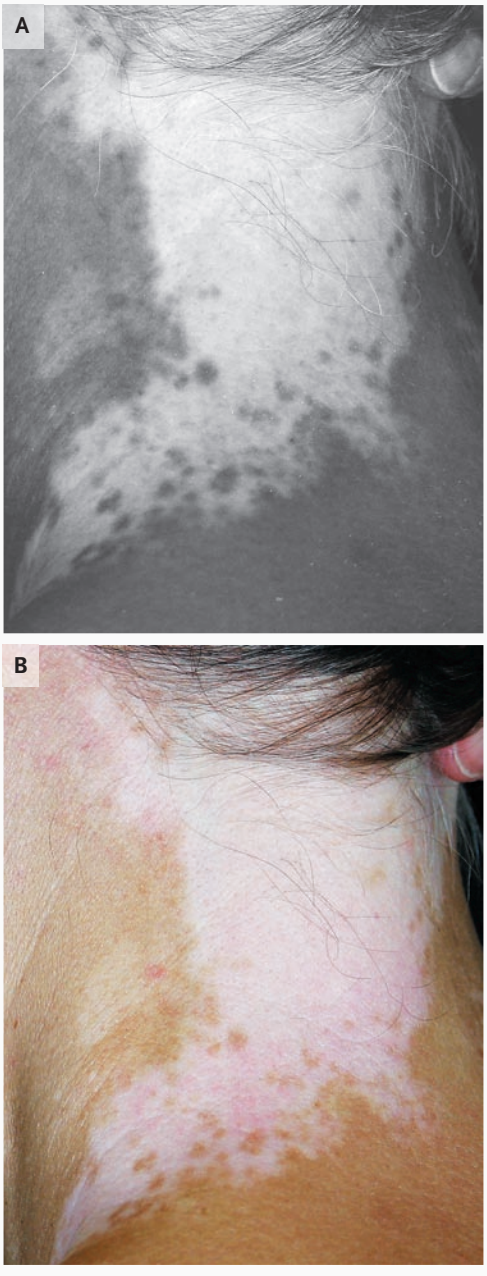

Figure 2. Wood's Lamp Examination.

Wood's lamp is a handheld ultraviolet A irradiation device that emits at approximately 365 nm. Examination with Wood's lamp is best performed in a completely dark room. The examiner should allow at least 30 seconds for adapting to the darkness before starting the examination. Wood's lamp provides bright reflection of white patches and enhanced details on intermediate pigment tones (Panel A), as compared with normal light (Panel B). Some lamps incorporate a magnifying lens that is useful in evaluating terminal and vellus pigmentation of hair. For patients with darker skin types, Wood's lamp examination is less useful.

among adults with vitiligo, repigmentation was significantly more likely with narrow-band UVB radiation than with PUVA (occurring in 67% of patients vs. 46% at 4 months). After 1 year of narrow-band UVB treatment, 63% of patients had more than 75% repigmentation.[21] The same narrow-band UVB regimen applied to children (mean age, 9.9 years) for up to 1 year resulted in more than 75% repigmentation in 53% of patients; the disease stabilized with therapy in 80% of the children who had active disease at study entry.[22] The superiority of narrow-band UVB treatment was also confirmed in a double-blind, randomized trial in which it was compared with oral PUVA in 50 patients with nonsegmental vitiligo[23]; an improvement of more than 50% was noted after 48 sessions in 53% of patients treated with narrow-band UVB as compared with 23% of those treated with PUVA. The color match of repigmented skin was considered to be excellent in all patients treated with narrow-band UVB radiation but in only 44% of those treated with PUVA. Patients in the PUVA group also had greater erythema and had nausea (due to ingestion of oral psoralen).

Narrow-band UVB therapy is usually given twice weekly — but not on 2 successive days — in sessions lasting 5 to 10 minutes. The simplest approach is to use a fixed starting dose (0.21 J per square centimeter), regardless of the skin phototype, and to increase the dose by 20% with each session until the minimal erythema dose (i.e., the lowest dose that results in visible erythema on depigmented skin at 24 hours) has been reached.[24] The optimal dose may differ at different sites; areas responsive to lower doses can be shielded until the optimal dose has been reached for areas requiring higher doses.[24] In two studies,[21,24] twice-weekly treatment with narrow-band UVB for 1 year in patients with nonsegmental vitiligo resulted in repigmentation of 75% of affected areas in 48%[24] and 63%[21] of patients. At least 3 months of treatment is warranted before the condition can be classified as nonresponsive, and approximately 9 months of treatment is usually required to achieve the maximal repigmentation. There is no apparent relationship between the degree of initial depigmentation and the response to narrow-band UVB treatment,[21] but the duration of disease is inversely correlated with the degree of treatment-induced repigmentation.[24] The best results are achieved on the face, followed by the trunk and limbs. The poorest outcomes have

Table 2. Major Differential Diagnoses for Nonsegmental Vitiligo.

Diagnosis	Features
Inherited or genetically induced hypomelanoses	Depigmentation present at birth, but hypopigmented patches may not be noticeable until after first exposure to sun, sometimes in second or third year of life; positive family history is common
Piebaldism	White forelock, midline depigmentation of anterior body, bilateral shin depigmentation; autosomal dominance
Tuberous sclerosis	Small or larger (ash-leaf) white spots, seizures, typically later appearance of other cutaneous symptoms (e.g., shagreen patches, angiofibromas); autosomal dominance
Ito's hypomelanosis	Linear distribution, unilateral or bilateral pattern of hypopigmented streaks; sporadic; chromosomal or genetic mosaicism (involving blood or skin cells)
Waardenburg's syndrome	White forelock, hypertelorism, deafness (varies according to genotype); possible association with congenital megacolon (Hirschsprung's disease)
Postinflammatory hypopigmentation	Occurs in inflammatory disorders accompanied by increased epidermal turnover (e.g., psoriasis, atopic dermatitis), in lichenoid–cytotoxic infiltration of epidermal basal layer (e.g., lichen planus, toxic drug reactions), and in scleroderma; clinically distinguished by identification of the primary skin disease (e.g., scalp or plaque psoriasis, flexural dermatitis for atopic dermatitis, scleroderma plaques), but may coexist with primary disease; in genital areas, lichen sclerosus may resemble vitiligo or be associated with true vitiligo; biopsy is useful in cases that are difficult to diagnose
Paramalignant hypomelanoses	
Mycosis fungoides	May present with skin depigmentation in dark-skinned patients; clinical diagnosis may be difficult in the absence of signs of inflammation and skin infiltration; biopsy results are diagnostic
Melanoma	Vitiligoid changes range from halo of depigmentation around a cutaneous melanoma (malignant Sutton's phenomenon) to more widespread vitiligoid changes; under Wood's lamp, the margins of such vitiligoid lesions are usually less distinct than in common vitiligo, and depigmentation is usually incomplete
Parainfectious hypopigmentation	
Tinea versicolor	Can cause vitiligoid changes, generally after treatment in the absence of re-exposure to UV light; the distribution and shape of the lesions and the presence of scaling and green fluorescence of untreated lesions allow a definite diagnosis
Indeterminate leprosy	Manifested as hypochromic patches that are hypoesthetic to light touch
Acquired macular hypomelanosis	Seen in young adults and frequently referred to as a recalcitrant pityriasis versicolor; white macules are present on the trunk, with more marked involvement on the lower back and axillae; *Propionibacterium acnes* is a suspected cause of depigmentation
Post-traumatic leukoderma	May occur after deep burns or scarring in which hair follicles are removed entirely or in which the bulge area containing melanocyte precursors is destroyed; can be difficult to distinguish from true vitiligo when scarring is not obvious; may also occur after toxic epidermal necrolysis
Melasma	May be confused with vitiligo when hyperpigmented facial lesions surround normal but hypochromic-looking skin; the pattern of relative hypopigmentation is usually different from that of vitiligo, and examination of other body sites allows a definitive diagnosis
Occupational and drug-induced depigmentation	
Occupational	A subtype of vitiligo triggered by occupational exposure, which evolves from contact depigmentation (generally caused by a phenolic–catecholic derivative*) to a generalized phenomenon; may be difficult to distinguish from other cases of vitiligo
Drug-induced	Can result from use of systemic drugs (e.g., chloroquine, fluphenazine, physostigmine, imatinib); in rare cases topical imiquimod may also cause vitiligoid depigmentation

* Possible sources of phenolic–catecholic derivatives[9] include adhesives, de-emulsifiers used in oil fields, deodorants, disinfectants, duplicating paper, formaldehyde resins, germicidal detergents, insecticides, latex gloves, motor-oil additives, paints, photographic chemicals, plasticizers, printing ink, rubber antioxidants, soap antioxidants, synthetic oils, varnish, and lacquer resins.

been noted for lesions on the hands and feet. Relapses are common at all sites; in approximately two thirds of patients, depigmentation recurs within a year in repigmented areas.[23]

The response of segmental vitiligo to narrow-band UVB treatment is at best limited.[24] Preliminary data suggest that the use of targeted high-exposure doses of UVB radiation (excimer laser or monochromatic excimer lamp, both at 308 nm), which may reach deeper targets (e.g.,

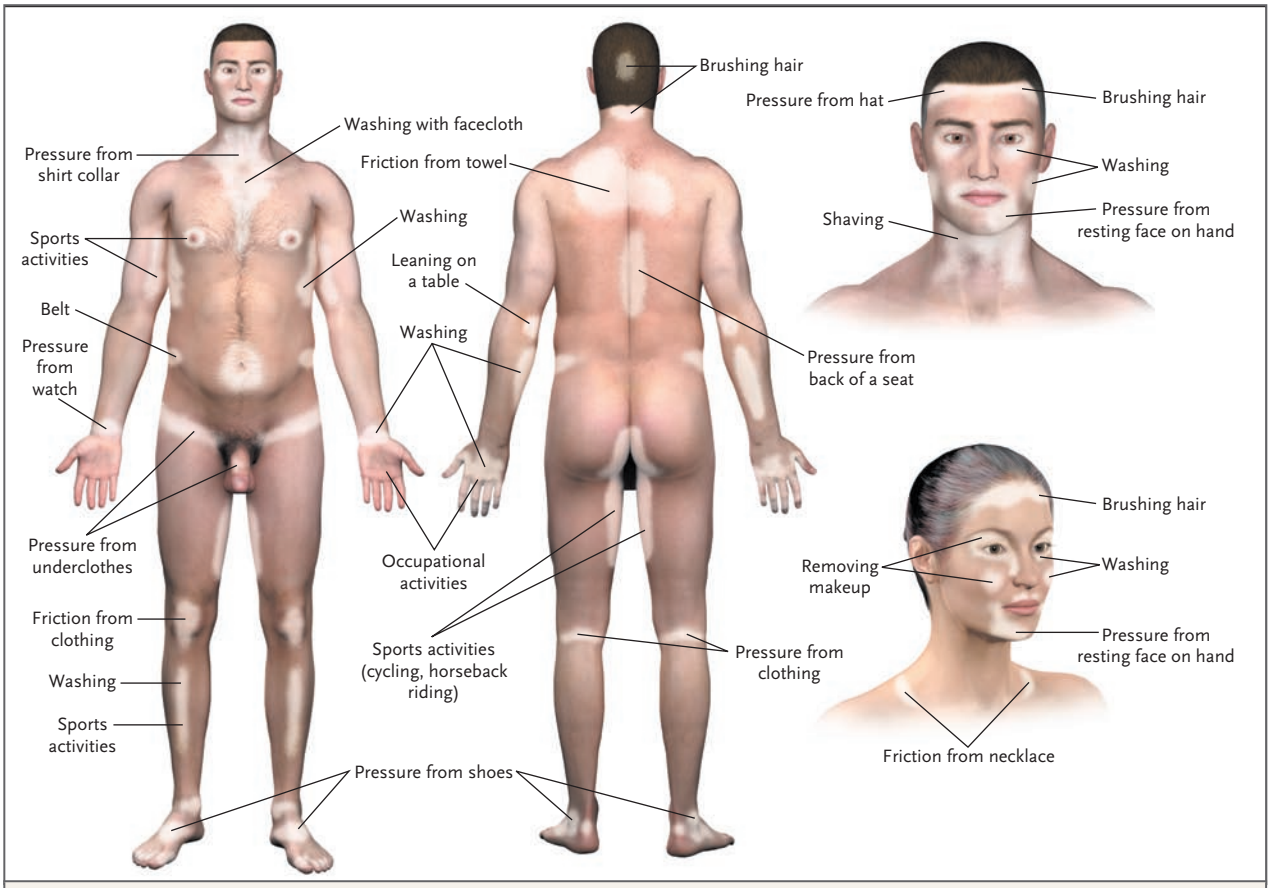

Figure 3. Koebner's Phenomenon.

In Koebner's phenomenon, vitiligo patches develop in an isomorphic response to the friction or pressure resulting from such common activities as brushing hair, drying skin with a towel, and wearing a belt or watch.

amelanotic melanocytes of the hair follicle) while minimizing irradiation of uninvolved skin, may improve outcomes for patients with limited areas of nonsegmental vitiligo.[25-27] The red light emitted with helium–neon laser phototherapy has also been reported to promote repigmentation in patients with segmental vitiligo, although data are limited.[28]

Topical Therapies

Topical therapies, including corticosteroids and calcineurin inhibitors, may be effective in cases of nonsegmental or segmental vitiligo in which the disease is localized. Combined topical and ultraviolet-light treatments are often considered when there has been no response to phototherapy alone after 3 months or when the goal is to accelerate the response and reduce cumulative exposure to ultraviolet light. As compared with PUVA, which promotes a predominantly perifollicular pattern of repigmentation, topical corticosteroids and calcineurin inhibitors result in more diffuse repigmentation, which occurs more quickly but is less stable.[29] A systematic review of randomized trials and case series showed that class 3 (potent) topical corticosteroids (e.g., betamethasone) were significantly more effective than placebo in treating localized vitiligo, resulting in more than 75% repigmentation in 56% of patients.[18]

Topical calcineurin inhibitors are generally preferred for face and neck lesions because they do not cause skin atrophy[30] and can promote repigmentation without inducing immunosuppression.[31] Their efficacy is enhanced by occlusion with a polyethylene foil[32] or exposure to ultraviolet radiation delivered by high-fluency UVB devices,[25] but it is not clear whether conventional narrow-band UVB treatment enhances efficacy.[33]

Table 3. Management Strategies for Vitiligo in Adults.*

Type of Vitiligo	Usual Management
Segmental and limited nonsegmental (<2–3% body-surface involvement)	First line — avoid triggering factors, use local therapies (topical corticosteroids, calcineurin inhibitors) Second line — use localized narrow-band UVB therapy, especially excimer monochromatic lamp or laser Third line — consider surgical techniques if repigmentation cosmetically unsatisfactory on visible areas
Nonsegmental (>3% body-surface involvement)	First line — stabilize with narrow-band UVB therapy for at least 3 months, with optimal duration of at least 9 months if there is a response; combine with topical therapies, including possible reinforcement with targeted UVB therapy Second line — consider systemic corticosteroids or immunosuppressive agents if there is extension under narrow-band UVB therapy, but the data supporting this approach are limited Third line — consider surgical techniques in areas showing no response for at least 1 year, especially areas with high cosmetic value (e.g., the face); however, Koebner's phenomenon may adversely affect graft survival; relative contraindication in areas such as dorsum of hands Fourth line — consider depigmentation techniques (monobenzyl ether of hydroquinone or mequinol alone or associated with Q-switched ruby laser) when more than 50% of treated area does not respond or when area is highly visible, as on face or hands

* A no-treatment option can be considered in patients with a fair complexion, after discussion. Phototherapy has limited feasibility in children younger than 7 years of age, and surgical techniques are rarely proposed before puberty.

More data are needed to determine the effectiveness of combining calcineurin inhibitors with UVB or other sources of light, such as the red light emitted by helium–neon laser.[34] The usefulness of these agents as the sole form of therapy for sites protected from the sun, such as genitals and nipples, requires further study. Concerns have been raised about the risks of cutaneous or extracutaneous cancer with the use of topical calcineurin inhibitors, but data providing strong support for such an association are lacking.[35] It is unclear whether the use of a topical corticosteroid in combination with UVB radiation is superior to UVB radiation alone.

Surgery

Surgical methods, including minigrafting,[36] transplantation of autologous epidermal cell suspensions,[37] application of ultrathin epidermal grafts,[38] and a combination of these approaches, are used in some cases of focal or segmental vitiligo if medical approaches fail (see Fig. 2 in the Supplementary Appendix). Ultraviolet-light therapy is generally combined with these methods. Patients with nonsegmental vitiligo are considered good candidates for surgical treatments, depending on their availability and cost, if the disease has stabilized (during the previous 1 to 2 years) and is limited in extent (covering no more than 2 to 3% of body-surface area). The survival of transplanted melanocytes is more likely in segmental vitiligo than in nonsegmental vitiligo, since the grafted cells can be harvested from disease-free areas. Koebner's phenomenon limits efficacy (on the hands in particular). In one randomized trial involving patients with nonsegmental vitiligo who were carefully selected for stable disease, the combination of cellular transplantation plus treatment with ultraviolet light resulted in repigmentation of at least 70% of the treated area as compared with a near absence of repigmentation in the group treated with a noncellular dressing plus ultraviolet light.[39]

Other Therapies

Topical remedies can be used to mask skin disfigurement on a temporary, semipermanent, or permanent basis. They include self-tanning agents; stains; dyes; whitening lotions; tinted cover creams; powder, liquid, and stick foundations; fixing powders and sprays; cleansers; semipermanent and permanent tattoos; and dyes for white hair on the face and head. Dihydroxyacetone (DHA) is the most frequently used self-tanning agent (for recommendations on the use of DHA, see Table 1 of the Supplementary Appendix). The higher the concentration, the better the response observed, particularly in patients who have darker

phototypes.[40] Self-tanning interventions may improve quality of life.[41] Chemical or laser depigmentation is an option in a small subgroup of carefully selected patients, but the results are variable.[42]

Sunscreens are needed if there is a risk of sunburn on nonphotoprotected skin, but they are not recommended on a routine basis because moderate sun exposure (heliotherapy) provides benefits associated with exposure to ultraviolet light, and because there is a theoretical risk that the friction caused by repeated application of sunscreen might exacerbate the disease. Depigmented skin in vitiligo tends to show increased tolerance to UVB light over time (photoadaptation), with the extent of tolerance based in part on skin phototype.[43]

AREAS OF UNCERTAINTY

The basic mechanisms of melanocyte loss and those limiting follicular or marginal repigmentation remain unclear. Development of a formal system for staging skin inflammation in rapidly progressing disease would be helpful in guiding decisions about more aggressive interventions. Additional randomized trials using both objective and patient-oriented measures are needed to compare the effectiveness of various therapies and to guide optimal management of the disease. Longer-term follow-up is needed to better establish the safety of UVB therapy and calcineurin inhibitors.

Topical calcipotriene (a vitamin D_3 analogue) is sometimes used for localized disease, but trials have indicated that it has limited or no effect when used alone and that it results in at most a minor increase in repigmentation when used in combination with ultraviolet radiation or topical corticosteroids.[44] Data on the efficacy of topical antioxidants and natural health products are limited. Data from open-label studies have suggested that the use of systemic corticosteroids may arrest disease progression,[45,46] but data from randomized trials of this and other systemic immunosuppressive agents are lacking.

GUIDELINES

Guidelines for the management of vitiligo in adults and children have been published by the British Association of Dermatologists,[47] and guidelines for surgery are available from the Indian Association of Dermatologists, Venereologists, and Leprologists Dermatosurgery Task Force.[48] The recommendations in this article are generally consistent with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

In a case such as the one in the vignette, the initial assessment should focus on the extent of disease, possible aggravation of disease due to friction or pressure on affected areas, and the possibility that other associated autoimmune diseases — in particular, thyroid disease — may be involved. Attention must be paid to the psychological effects of the condition and to whether a referral is needed for psychological support. Patients should be informed that vitiligo is a chronic, relapsing disorder, that repigmentation is a slow process, and that reactivation of the disease in different body regions or the reappearance of lesions in treated regions may occur. Narrow-band UVB radiation has proved to be effective in the treatment of widespread disease, and we recommend it as first-line therapy. In the case of localized disease, we recommend starting treatment with a potent topical corticosteroid or topical calcineurin inhibitor; on the face, calcineurin inhibitors are currently preferred because of the potential side effects of prolonged application of corticosteroids, although the long-term safety of calcineurin inhibitors requires further study. Camouflage techniques may also be helpful, particularly in dark-skinned patients with lesions on their face or hands. Cellular transplantation, or grafting, is an option in specialized centers for selected patients with stable and limited lesions that are unresponsive to other forms of therapy.

An audio version of this article is available at NEJM.org

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